NON-TECHNICAL ABSTRACT

When inflammation occurs in the lungs, lung cells are injured in part by the release of enzymes from some white blood cells which digest proteins. Normally, a protein present in the lungs counteracts the damaging enzymes; this protein is called alpha-1 antitrypsin (AAT). Some people inherit a deficiency of AAT because the gene responsible for producing it is defective. These patients develop emphysema at an early age, presumably because the white blood cell enzymes digest the lungs. Also, when the lungs are injured as a result of blood stream infection, trauma or some other causes, this, too, appears to be in part because the white blood cells release the same enzymes which digest lung cells. In this case, the person may have normal amounts of AAT, but so much of the enzymes are released that this normal defense is overwhelmed. In either case (either AAT deficiency or acute lung injury), if lung cells could be genetically engineered to make increased amounts of AAT, the lung might be protected from injury. We propose to give the gene for AAT imbedded in some DNA which will cause the gene to make the AAT protein in large amounts to the lungs of humans. We will use DNA in a form which does not incorporate into host DNA (a circular form of DNA called a plasmid) and we will combine the plasmid with small fat globules called liposomes. These special liposomes are constructed so that they associate by charge interaction with DNA and escort the DNA into cells so that it can be expressed. In order to expose patients to minimal risk, we propose to begin by putting the plasmid/liposome into a lung that is going to be removed for some other reason (usually cancer) 2-3 days before surgery and then obtaining some of the removed lung at surgery in order to see whether there was any damage and also whether the gene we gave is working in the lungs. In some patients with AAT deficiency, we propose to give the plasmid/liposome to one nostril and then wash the nostrils each day to measure AAT in the fluid as a measure of whether the gene we gave is working. Some cells will also be taken from the nose by scraping and tested for the administered gene function. We have shown in cells in culture and in animals that the plasmid/liposome technology works and is safe; these studies will determine whether that is also true in the human respiratory tract. This information is critical to proceeding to any tests of therapeutic effectiveness of this approach.